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Blocking Lymphocyte Localization to the Gastrointestinal Mucosa as a Therapeutic Strategy for IBD

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Abstract

Lymphocyte migration (homing) to specific tissues has an important role during protective and pathological immune responses, including inflammatory bowel diseases (IBDs). Lymphocytes use integrin α4β7 and the chemokine receptor CCR9 to localize to the gastrointestinal (GI) mucosa; their respective ligands, MAdCAM-1 and CCL25, are displayed on endothelial cells in intestinal post-capillary venules. Whereas GI-homing receptors are required for lymphocyte migration to the intestine in the non-inflamed steady state, their role during inflammation is a matter of debate. Reagents designed to block interactions between these receptors and their ligands have had variable degrees of success in animal models of IBD and patients. We discuss the mechanisms involved in lymphocyte localization to the intestinal mucosa and how they can be applied to therapy for IBD.

Introduction

Lymphocytes localize to specific tissues during the protective immune response and in inflammatory disorders. Learning how these cells localize to different organs is important for understanding basic immunology as well as disease pathogenesis.

Circulating lymphocytes are exposed to extreme shear forces so they do not randomly adhere to endothelial cells; 1 instead, they express adhesion receptors for ligands expressed on endothelial cells. Adhesion usually takes place in post-capillary venules via a multistep process. First, lymphocytes are captured and loosely adhere to the endothelial cells (tethering and rolling, respectively), a step that usually requires selectins and their ligands, although the integrins α4β7 and α4β1 can also contribute to this step in some tissues. While lymphocytes are rolling they can be stimulated, generally via chemokine receptors (activation), which increases integrins' binding affinity and avidity. Integrin activation

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causes the lymphocytes to adhere to the endothelium (sticking) and then extravasation into non-inflamed or inflamed tissues.

Lymphocyte migration and adhesion to specific tissues are determined by the combination of receptors involved in each step, rather than a single receptor and adhesive molecule. The diversity of receptors use in each step of the adhesion process allows for versatile and tissue-specific localization of lymphocytes, making lymphocyte adhesion amenable to modulation for therapeutic purposes.

The mechanisms that regulate lymphocyte homing to different tissues have been reviewed; [2-4] we focus on lymphocyte migration to the gastrointestinal (GI) mucosa and discuss how this process might be modulated in patients, to reduce GI inflammation.

Compartmentalized homing to the intestine

Naïve T and B cells constantly transit between the blood and secondary lymphoid organs (SLO), such as spleen, lymph nodes and Peyer's patches (PP). Upon activation in SLO, naïve lymphocytes become effector and/or memory T and B cells and express receptors that control their migration to extra-lymphoid tissues such as the skin, GI lamina propria, central nervous system (CNS), liver, and lungs [5].

Whereas migration to SLO occurs through the mechanism described above, lymphocyte migration to some extra-lymphoid tissues requires expression of specific receptors. T-cell localization the GI mucosa and the skin—the largest surfaces in the body that are exposed to the external environment—has been well characterized. T-cell migration to the skin requires ligands for P- and E-selectins, CCR4, and the integrin lymphocyte function antigen (LFA)-1 [6].

In contrast to the skin, migration of T and B cells to the small intestine requires the integrin α4β7 and CCR9, whose induction depends on the vitamin A metabolite *all-trans* retinoic acid (RA) [3] (Figure 1). Localization to colon partially requires α4β7, but not CCR9; [7] the chemokine receptor(s) required for leukocyte migration to the colon have not been identified.

The ligand for CCR9, CCL25/TECK, is differentially distributed in a proximal-to-distal gradient in the small bowel; CD8+ T cells localize to the ileum partially via CCR9-independent mechanisms (Figure 1) [7]. Alternative candidates for T-cell migration to the small bowel include CXCR3 and CXCR4, whose ligands (CXCL10 and CXCL12, respectively), are expressed in the GI mucosa [8]. Consistent with an in vivo role for these alternative chemokine pathways, *CXCR3*$^{-/-}$ mice have lower numbers of CD8+ intestinal epithelial cells in the lamina propria; [9] blocking the interaction between CXCR4 and CXCL12 inhibits entry of T cells to the small intestine in steady-state and inflammatory conditions [10].

Localization of lymphocytes to the colon differs in some ways from migration to the small bowel—it requires either α4β7 or α4β1, but not CCR9 [6, 11]. The ligand for α4β7, MAdCAM-1, is expressed in small bowel and colon, whereas CCL25 is expressed in only the small bowel [12, 13]. Moreover, whereas migration to the small intestine was impaired in *CCR9*$^{-/-}$ and β7 integrin chain-deficient (*β7*$^{-/-}$) T-helper (Th)17, homing to the colon was reduced in only the *β7*$^{-/-}$ Th17 cells [14]. Transfer of *β7*$^{-/-}$ Th17 cells into SCID mice induced less inflammation in the small and large bowel than transfer of wild-type Th17 cells (Table 1), whereas transfer *of CCR9*$^{-/-}$ Th17 induced less inflammation than wild-type cells in only the small bowel [14]. Together, these data indicate that CCR9 is required for T-cell migration

and pathogenicity primarily in the small intestine, whereas α4β7 is required for T-cell migration and pathogenicity in the small bowel and colon.

Migration of T cells to the intestinal mucosa also depends on their specific subset and phenotype. Recently activated CD8+ T cells require CCR9 for migration to the small bowel, whereas effector CD4+ T cells are less dependent on CCR9 for homing into this GI compartment[15]. Moreover, homing *of CCR6*$^{-/-}$ Th17 cells to PP and small bowel was significantly reduced, compared to wild-type Th17 cells, whereas homing of Th1 or Foxp3^{+} regulatory T cells (T_{REG}) to these compartments did not require CCR6 [16]. RA induces α4β7 and CCR9 on T_{REG} [1718]; however, mice given diets that did not contain vitamin A (and therefore lack RA synthesis) did not have decreased numbers of T_{REG} in the small bowel, although Th17 cells were markedly reduced in this compartment [19]. Moreover, T_{REG} isolated from mice depleted of dietary vitamin A were equally efficient in suppressing ileitis as T_{REG} from mice on a vitamin A sufficient diet (or that received extra vitamin A)[20]. However, these studies did not discriminate between thymus-derived or inducible T_{REG}. Further studies are needed to determine the in vivo roles of RA in localization of T_{REG} in the GI mucosa and their immunoregulatory functions there.

Another example of differential gut-homing requirements is cells that secrete immunoglobulin (Ig)A (IgA-secreting cells). CCR10 is expressed primarily by IgA-secreting cells, whereas cells that secrete antibodies against IgG or IgM do not express this receptor [21]. Moreover, IgA-secreting cells require CCR10 to localize to the intestine, although CCR10 is not expressed on gut-associated T cells [4, 21]. In addition to CCR10, IgA-secreting cells also express CCR9; mice deficient in this receptor have reduced numbers of these cells in the small intestine [22]. Interestingly, blocking CCR9 prevented localization of IgA-secreting cells to the small bowel, whereas blocking either CCR10 or its mucosal ligand, CCL28, impaired their localization to small and large bowel [23]. Similar to T cells, RA was sufficient to induce CCR9 and α4β7 (but not CCR10) on activated B cells and mice depleted of vitamin A had very low numbers of small bowel IgA-secreting cells. [19, 24, 25]

Aberrant recruitment of lymphocyte in IBDs

IBDs, which include Crohn's disease (CD) and ulcerative colitis (UC), are associated with a massive influx of immune cells into the GI tract. During disease development, altered production of pro-inflammatory cytokines induces expression of alternative adhesion receptors and chemokines on intestinal endothelial cells, which might allow lymphocytes to migrate to the intestine without expression of the receptors that normally regulate their localization in that compartment [11]. These alternative pathways of lymphocyte recruitment might have important implications for IBD therapy.

Studies of animal models and human tissues have indicated the role for gut-homing effector T cells in IBD pathogenesis. In experimental models of IBD, MAdCAM-1 is upregulated in the intestinal lamina propria.[26-2829] Similar MAdCAM-1 upregulation is observed in active inflamed tissues from patients with CD or UC, which is associated with increased numbers of α4β7^{+} T cells, compared with normal tissues [30, 31]. Deficiency of β7 integrin subunit inhibits inflammation in a mouse model of CD [32] and antibodies against β7 or MAdCAM-1 reduced inflammation in mice with TNBS-induced or cell transfer-induced colitis [33,34] (Table 1). Blocking α4 or α4β7 reduced colitis in a non-human primate model of IBD [35, 36]. Additional mechanistic insights have come from studies of SAMP1/YitFc mice, which spontaneously develop CD-like ileitis. Although SAMP1/YitFc mice deficient in β7 have reduced intestinal inflammation [37], antibodies that block α4β7 or MAdCAM-1 did not reduce the inflammation; only combined blockade of VCAM-1 and MAdCAM-1 significantly improved ileitis [29].

Blocking α1β1, a collagen-binding integrin that is upregulated in inflamed tissues, reduced TNBS-induced colitis in mice [38]. Results from mice with dextran sodium sulphate (DSS)-induced colitis have varied results—some studies reported that blockers of MAdCAM-1 reduced inflammation,[33, 39, 40] whereas others showed that development of colitis required α4β1–VCAM-1 and β2–ICAM-1 interactions, but not α4β7–MAdCAM-1 [41, 42]. Pathogenic effector T cells might not require only interaction between lymphocyte α4β7 and epithelial cell MAdCAM-1 to promote chronic inflammation, but other integrins that mediate immune cell localization during general inflammation might fulfill redundant roles in intestinal pathology.

SAMP1/YitFc mice have increased numbers of IgA-secreting cells in the MLN and LP [43]. Adoptive transfer of B cells and T cells from SAMP1/YitFc into SCID mice increased ileitis, compared with transfer of only T cells [43]. Moreover, B cells required α4β7 to exacerbate ileitis [37], indicating that B-cell localization to the GI tract might also be involved in IBD pathogenesis.

T_{REG} cells are believed to prevent or even cure intestinal inflammation, based on studies from different models of IBD. However, the precise role of α4β7 and CCR9 in trafficking and function of T_{REG} cells during GI inflammation is unclear. T_{REG} cells seem to require β7-independent pathways—rather, those that involve CCR7 and CCR4 —for their immune suppressive functions and to prevent colitis [44-46]. These alternative migratory pathways might allow T_{REG} cells function in lymphoid compartments, such as prophylactic suppression before the onset of inflammation in MLN or PP. However, T_{REG} cells might need GI homing receptors to suppress immune activity in the lamina propria during active inflammation [47], which is probably most relevant for development of therapeutics.

CCL5 and CCR5 are also up-regulated in experimental models of ileitis and mediate the specific recruitment of T_{REG} cells and some subsets of effector CD4+ T cells[48]. These alternative chemokine pathways could account for the observation that blocking CCL25 or CCR9 is only effective at early stages of disease, even though expression of CCL25 increases in the small bowel of patients with CD. [49] Other, perhaps non GI-specific, chemokine signals might mediate lymphocyte homing at later stages during inflammation [50]. Human lamina propria and intraepithelial lymphocytes also express CXCR3, CX3CR1, and CCR2, and levels of their ligands are increased in tissues of patients CD [51]. Moreover, recruitment of T cells, monocytes, and DC to the inflamed mucosa might also involve CX3CL1 and its receptor CX3CR1, which contributes to pathogenesis of IBD [52-54].

Some of the extra-intestinal pathologies associated with IBD might arise from aberrant homing of immune cells. For instance, MAdCAM-1 and CCL25 are upregulated in the liver during primary sclerosing colangitis (PSC), a chronic disease characterized by progressive inflammation and scarring of the bile ducts. PSC has been associated with UC in epidemiologic studies [55].

Therapies for IBD

Patients with IBD usually require life-long therapy with corticosteroids and other immunosuppressive drugs. Choice of therapy depends on the primary clinical goal (induction or maintenance of remission), the extent and severity of disease, the response to current or prior treatments, and the occurrence of side effects (summarized in Supplementary Table 1A). Many drugs for IBD can have serious adverse effects, and some patients become refractory to treatment during disease progression and require surgery. Therefore, new therapeutic approaches, that target specific inflammatory mediators, are needed.

Although the primary causes of IBD are not clear, many molecules that are involved in disease pathogenesis have been identified as targets for therapy. Therapeutics that have been developed include inhibitors of T-cell activation, co-stimulatory pathways, pro-inflammatory cytokine receptors, Th1 polarization, cytokines and their regulatory proteins, growth hormone, and growth factors (Supplementary Table 1B, C).

Although many of these biologic agents showed efficacy in preclinical studies, most of them have not shown efficacy in clinical trials, or have caused significant side effects [56]. Antibodies to the cytokine TNF-α have been the most effective, and are currently used to treat patients with refractory moderate-to-severe active CD or UC. Infliximab binds the soluble bioactive and membrane-bound forms of human TNF-α and reduces its toxicity. Although Infliximab is effective in reducing the symptoms of IBDs, its immunosuppressive effects predispose patients to infections and increase risk of malignancies, such as lymphomas [57, 58].

Blocking adhesion receptors

Molecules that mediate lymphocyte localization to the GI mucosa, in the steady state or during development of inflammatory diseases such as IBDs, are attractive targets for drug development. Antibodies or compounds that selectively block homing receptors, [11] or reagents that sequester lymphocytes in secondary lymphoid organs (to prevent their migration to sites of inflammation), [59] have shown efficacy in animal models and in clinical trials for psoriasis [60, 61], asthma [62], graft-versus-host disease, [63] and multiple sclerosis [59].

Because α4β7 and CCR9 are the primary mediators of lymphocyte migration to the intestine, reagents that block their function should reduce inflammation in the intestinal mucosa, yet cause low levels of systemic immunosuppression. Agents developed for treatment of IBD disrupt interactions between LFA-1 and ICAM-1, α4β1 and VCAM-1, as well as α4β7 and MAdCAM-1 (Figure 2, Table 2).

The first successful clinical use of anti-ICAM-1 was in treatment of rheumatoid arthritis [64]. Antibodies against ICAM-1 or antisense oligonucleotides that disrupt expression of ICAM-1 showed efficacy in mouse models of IBD, including DSS-induced colitis and SAMP-1/Yit mice ileitis[65 66]. Interestingly, in SAMP-1/Yit mice, anti-ICAM-1 was only effective when administered in combination with anti-VCAM-1 or anti-α4 integrins, indicating redundancy between LFA-1/ICAM-1 and α4β1/VCAM-1 pathways during inflammation in mice. Clinical trials that investigated the effects of reagents against ICAM-1 in patients with IBD included investigation of Alicaforsen (ISIS 2302), an antisense oligonucleotide that prevents expression of ICAM-1. Whereas an early-stage clinical trial suggested a therapeutic potential for Alicaforsen in patients with mild-to-moderate active CD [67], two subsequent, larger, multicenter trials failed to demonstrate significant efficacy [68 69]. Despite this setback, patients treated with Alicaforsen, in an enema formulation, had significant improvements in distal UC in a randomized, placebo-controlled trial. [70] However, given the important role of LFA-1 interaction with ICAM-1 in leukocyte localization to many lymphoid and non-lymphoid tissues, as well as in T-cell activation, [11] it is likely that blockers of ICAM-1 will cause significant systemic immunosuppression.

Natalizumab is a recombinant, humanized, monoclonal IgG4 against α4; it inhibits MAdCAM-1 signaling through integrin α4β7 and VCAM-1 signaling through integrin α4β1 [71]. In placebo-controlled, randomized trials, 40% patients with moderate-to-severe CD responded to Natalizumab and went to remission, compared to 8% in the group that received placebo [72].

However, phase III clinical trials that included clinical response, remission, and maintenance as endpoints showed that the drug was more effective when given in combination with other immunosuppressants or before therapy with an anti-TNF-α reagent [73, 74]. Since blockers of α4 probably do not affect T cells that have already localized to intestinal tissues, Natalizumab might not be sufficient to reduce ongoing inflammation—its combination with other immunosuppressant drugs might be required. Natalizumab has also shown potential for treatment of UC, [75] probably due to its ability to block α4β7 and α4β1 (integrins involved in localization of lymphocytes to the colon).

Natalizumab has also been used to treat patients with multiple sclerosis, [76] based on the role of α4β1 interaction with VCAM-1 in leukocyte homing to the CNS and experimental allergic encephalomyelitis [77]. However, cases of progressive multifocal leukoencephalopathy (PML)—a rare and often fatal opportunistic infection of the CNS—have developed in some patients given Natalizumab (approximate incidence 1/1000), raising concerns about its safety [78, 79]. Sporadic cases of melanoma have also been reported in patients treated with Natalizumab, which might be associated with impaired immunosurveillance of the skin following α4β1 blockade [80, 81]. However, larger cohorts of patients that have received Natalizumab need to be studied to determine more precisely the incidence of these rare side effects. Similar safety concerns might also apply to an orally bioavailable inhibitor of α4 (AJM300), which has also shown to be effective in patients with active CD [82]. Some cases of PML also occurred in patients with psoriasis who were treated with Efalizumab, a monoclonal antibody against LFA-1 [83]. Reagents that selectively block homing of lymphocytes to the GI without affecting immunosurveillance in other tissues (including the CNS), are urgently required for IBD.

Vedolizumab (MLN-02) is a humanized monoclonal IgG1 against integrin α4β7. In a phase II trial in 181 patients with UC, remission rates were significantly higher among subjects treated with Vedolizumab than those given placebo [84]. Another placebo-controlled trial of 185 patients with mild-to-moderate active CD showed that Vedolizumab was significantly more effective than placebo at inducing remission in patients with CD [85].

A monoclonal antibody against MAdCAM-1 (Pf-0054,659, human IgG2) is being tested in a phase I/II clinical trial of patients with UC. Although the study includes a small number of patients, endoscopic examinations identified improvements among in patients treated with anti-MAdCAM-1, without major side effects [86].

Nevertheless, because α4β1 might also have a role in chronic intestinal inflammation [29, 41, 42], it is possible that selective targeting of α4β7 or MAdCAM-1 might not be as effective as reagents designed to block both α4 integrins.

Chemokines as therapeutic targets

The effects of blocking the interaction between CCL25 and CCR9 were demonstrated in SAMP-1/Yit mice with ileitis. Blocking either CCL25 or CCR9 during early stages of ileitis reduced inflammation, whereas no effect was observed when mice were given the reagents at later stages of disease progression [50]. Moreover, administration of CCX282 (Traficet-EN), an orally bioavailable antagonist of CCR9, reduced the inflammatory response in mice when given before or after gut inflammation induced by TNF-α overexpression [87].

CCX282 is being tested in trials of patients with CD and refractory celiac disease (Figure 2, Table 2); preliminary efficacy and safety evaluations look promising [88]. In a phase II trial, 74 patients with CD were given either CCX282 or placebo for 28 days. Fifty-eight percent of patients had a significant reduction in CD scores, compared with 31% in the placebo group; in the CCX282 group, the effect that was associated with reduced levels of pro-

inflammatory cytokines and C-reactive protein [88]. A subsequent phase II/III trial showed significant improvement in the CCX282 group; disease scores were reduced in 81% of patients and 41% experienced clinical remission—effects that were maintained even upon withdrawal of corticosteroids [88].

Results from larger phase III trials of CCX282 for CD and UC are pending. Although the drug was generally well tolerated and not associated with an increased risk of infection, a large cohort of patients must be followed for long time period to exclude risk for rare diseases such as PML. The fact that CCX282 is orally bioavailable offers a clear advantage to parenteral therapies, decreasing the cost of the treatment, eliminating morbidity associated with parenteral administration, and potentially increasing compliance.

Interestingly, tolerogenic plasmacytoid DC also express CCR9, [89] which seems to be required for localization of these cells to the small bowel [90]. Inhibitors of CCR9 might affect migration of plasmacytoid DC and their tolerogenic functions in the intestine, with potential effects that should be considered and explored in models of IBD pathogenesis.

Conclusion

Although the exact cellular and molecular mechanisms of IBD pathogenesis are undefined, lymphocyte homing has an important role. Improved understanding of lymphocyte localization to the non-inflamed and inflamed intestinal mucosa has led to specific and effective therapies for IBD and improved the benefit–risk profile for patients.

Nevertheless, results from studies of animal models of IBD have identified alternative homing receptors that, in addition to α4β7 and/or CCR9, have roles in lymphocyte migration to the GI tract and might contribute to inflammation; these redundant homing pathways could account for the varying degrees of effectiveness of reagents that target GI-specific homing receptors in clinical trials. It is important to better define which receptors, adhesion molecules, and chemokine pathways contribute to chronic intestinal inflammation in humans. It is also important to determine the precise role of T_{REG} cells in intestinal inflammation and whether GI-specific reagents that interfere with lymphocyte adhesion affect T_{REG} functions. Combination therapies, which target more than one step in adhesion of lymphocytes to the intestinal epithelium, might be the most effective strategy for IBD. Combinations such as anti-α4β7 and antagonists of CCR9 could have additive effects to reduce inflammation in patients with IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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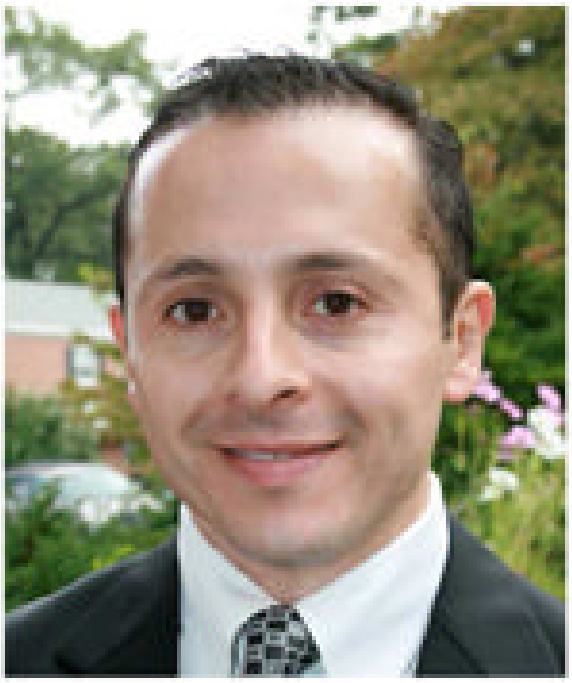
Biographies



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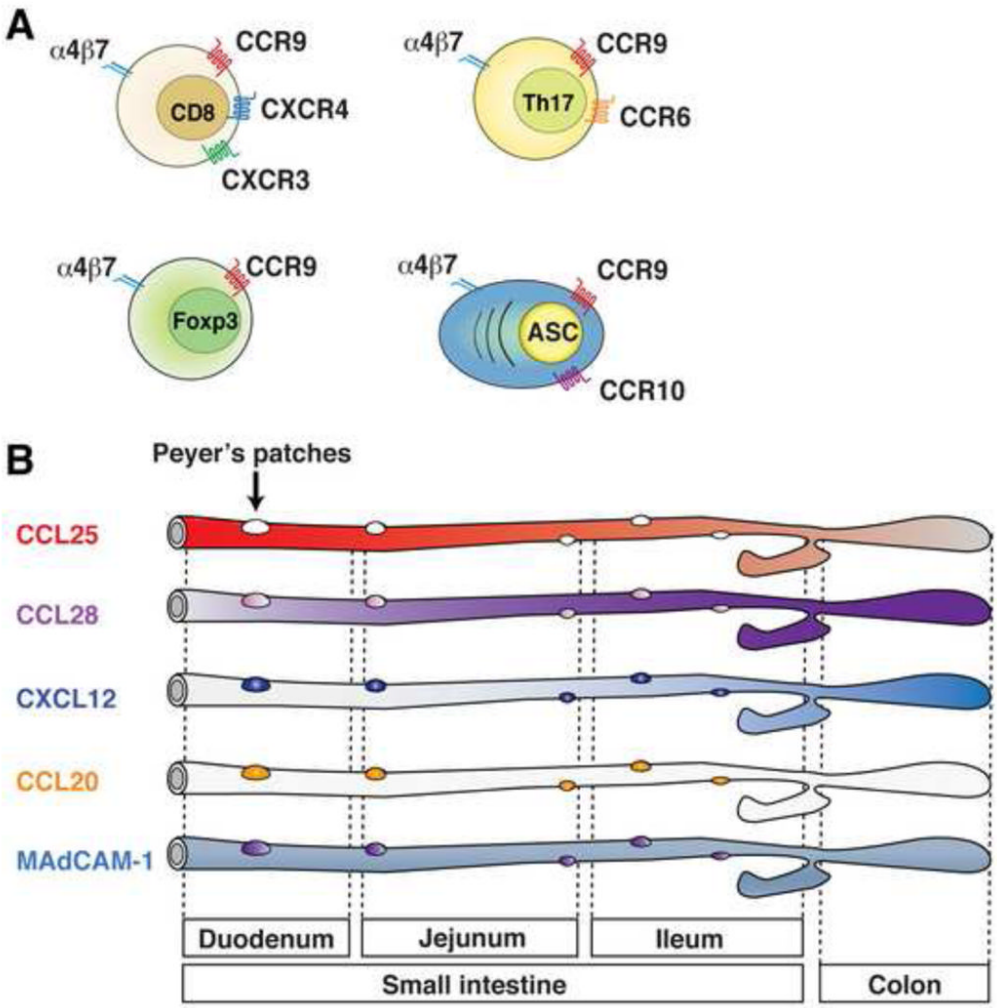

Figure 1. Different Lymphocyte Subsets Use Distinct Homing Receptors and Ligands to Localize to Specific Regions of the Intestine

A) Effector CD8+ T cells use CCR9 and α4β7, and possibly CXCR4 and/or CXCR3, to localize to the GI mucosa. Th17 cells might also use CCR6 to localize to small bowel and IgA-secreting cells use CCR10 to localize to GI and other mucosal tissue compartments. **B**) Expression of addressins varies throughout the intestine, even in the steady state. MAdCAM-1 is expressed along the whole intestine (small and large bowel) and it is upregulated during inflammation. CCL25, a ligand for CCR9, is expressed in a proximal-to-distal gradient in the small bowel but absent from the colon. CCL28, a ligand for CCR10, is expressed mostly in colon and other mucosal sites; it regulates localization of IgA-secreting cells, but not T cells. CCL20, a ligand for CCR6, is most highly expressed in Peyer's patches and the small bowel, but also it is upregulated in inflamed colon.

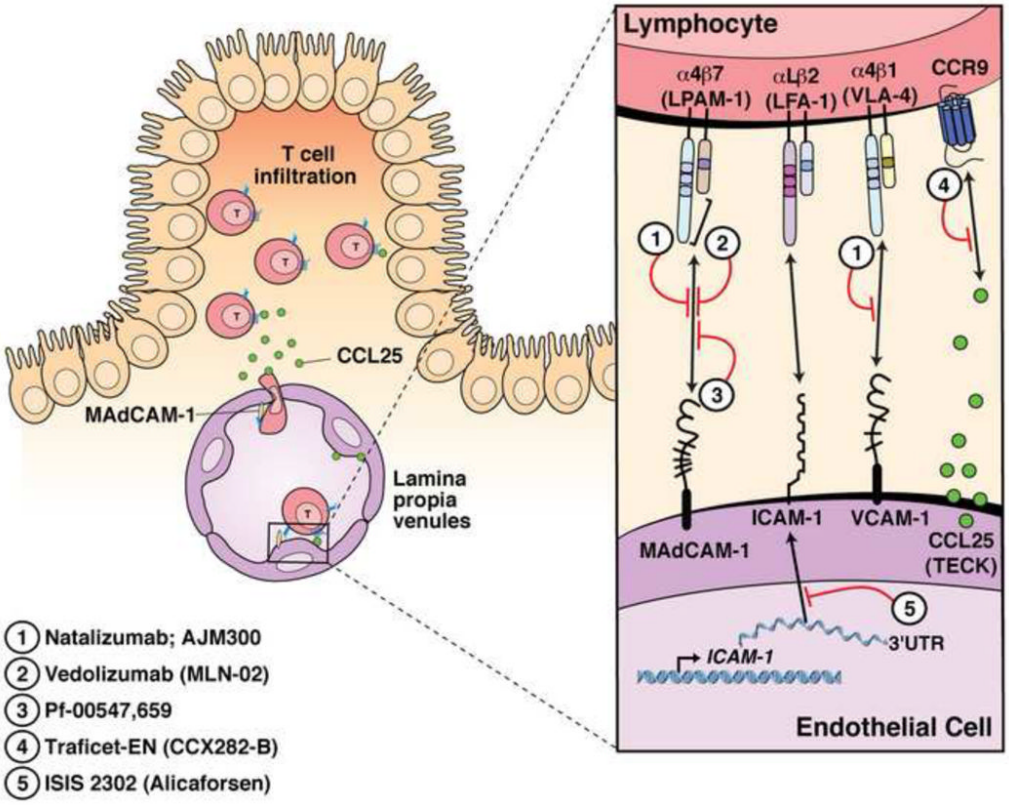

Figure 2. Interfering with Homing Receptors as Therapy for IBD

Natalizumab is a monoclonal antibody (mAb) that blocks the integrins α4β7 and α4β1, preventing their binding to MAdCAM-1 and VCAM-1, respectively. Similarly, AJM300 is an orally bioavailable antagonist of the integrin α4 subunit. The mAbs Velodizumab and Pf-00547,659 bind specifically to α4β7 and MAdCAM-1, respectively, blocking their interaction. Traficet-EN (CCX282-B) is an orally bioavailable selective antagonist of CCR9 that blocks its functional interaction with CCL25. Alicaforsen (ISIS 2302) is an antisense oligodeoxynocleotide that binds to the 3′ UTR portion of the *ICAM1* mRNA and prevents its translation.

Table 1

Role of gut-homing receptors in experimental IBD models

Model	Gut Segment	Pathogenic cells	Advantages	Limitations	Blocking homing receptors		Ref.
					α4β7 /MAdCAM-1	CCR9/CCL25	
Mouse DSS colitis	Colon	Innate immunity T/B cell independent (Occurs in RAG1$^{-/-}$mice)	Easy to set up, fast readout	Mostly colon inflammation, acute disease (can also be made chronic), T/B cell independent, little resemblance to human IBD?	Variable, with only some studies showing an effect in decreasing inflammation	Not determined (n.d.)	33, 39-42
Mouse TNBS colitis	Colon	Th1	Easy to set up, fast readout	Mostly colon, acute disease, little resemblance to human IBD?	Decreases colitis	n.d.	33
Naive CD4 T cell transfer into RAG1$^{-/-}$ or SCTD mice	Colon	Th1	Chronic disease, easy to set up, reproducibility	Mostly colon inflammation	Decreases colitis	n.d.	34
Gut-tropic Th1 7 cell transfer into RAG1$^{-/-}$ mice	Ileum and Colon	*Ex vivo* differentiated gut-homing Th17	Involvement of both small bowel (ileitis) and colon	Need transfer of *ex vivo* differentiated gut-homing Th17 cells	Decreases ileitis and colitis	Only decreases ileitis	14
Cotton-top tamarin	Colon	Th1?	Non-human primate	Cost, logistical limitations	Decreases colitis	n.d.	35, 36
TNF≅are mice (TNF-α overproduction)	Ileum	Th1	Affects small bowel (ileitis), chronic disease, model for human CD	Logistical (mice are non-commercially available)	Suppresses ileitis	No effect	32
Samp 1/Yit mice	Ileum	Th2, Th17, B cells	Affects small bowel (ileitis), chronic disease, model for human CD	Logistical (mice are non-commercially available)	Reduced ileitis in SAMP1/Yit β7$^{-/-}$mice Decreased ileitis when blocking both MAdCAM-1 and VCAM-1	Can prevent inflammation, but only early in disease	29, 37, 50

Table 2

Targeting homing receptors in IBD

Target Adhesion molecules	Name	Indication	Mechanism	Clinical Phase	Advantages	Side effects	Ref.
Human ICAM-1 antisense oligodeoxynucleotide	Alicaforsen (ISIS 2302)	CD, UC	Reduction of ICAM-1 protein expression	Phase II/III	Clinical improvements and well tolerated	Injection/infusion site reactions; Systemic immunosuppression	64, 65 66, 69, 70
Humanized IgG4 mAb anti-α4 integrin	Natalizumab	CD, UC	Inhibition of α4β7/ MAdCAM-1 interaction and α4β1/VCAM-1 binding.	Phase IV FDA-approved	Long-term clinical response and/or remission following the withdrawal of concomitant corticosteroids; well tolerated.	Rare cases of progressive multifocal leukoencephalopathy (PML); Rare cases of melanoma?	71-79
Orally bioavailable α4 integrin inhibitor	AJM300	CD (UC?)	Inhibition of α4β7/ MAdCAM-1 interaction and α4β1/VCAM-1 binding.	Phase II	Orally bioavailable	Same as Natalizumab?	82
Humanized IgG1 mAb anti-α4β7 integrin	Vedolizumab (MLN-02)	CD, UC	Inhibition of MAdCAM-1-mediated leukocyte adhesion	Phase II	Good clinical response and well-tolerated	Infusion reaction with angioedema, nausea and nasopharyngitis; Efficacy limited by development of anti-drug antibody	84, 85
Human IgG2 mAb anti-MAdCAM	PF-00547,659	UC (CD?)	Inhibition of α4β7/ MAdCAM-1 interaction	Phase I/II	Clinical improvements and well tolerated	No major side effects reported	86
Chemokine receptors							
Orally bioavailable antagonist for CCR9	Traficet-EN (CCX282-B)	CD GVHD? Celiac Disease? Intestinal transplant?	Inhibition of leukocyte chemotaxis to the ligand CCL25	Phase III	Clinical remission; well tolerated; orally bioactive; no risk of DTH reactions; no increased risk of systemic infection; no formation of anti-human Ab	No major side effects reported	50, 87, 88, 91